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NEW PROCEDURE TREATS
CONGENITAL HEART
DEFECT WITHOUT
OPEN-HEART SURGERY



ERRATIC HEARTBEATS
NO MORE



THE RAREST GIFT
- A NEW HEART



Prof Stuart Cook, Tanoto Foundation Professor of Cardiovascular Medicine at the SingHealth Duke-NUS Academic Medical Centre, and a Distinguished Clinician Scientist and Senior Consultant with the Department of Cardiology at the National Heart Centre Singapore.

Photo credit: Duke-NUS Medical School

BREAKTHROUGH DISCOVERY

UNCOVERING PROTEIN INTERLEUKIN 11 THAT
CAUSES FIBROSIS LEADING TO ORGANS DAMAGE

BREAKTHROUGH DISCOVERY UNCOVERING PROTEIN INTERLEUKIN 11 THAT CAUSES FIBROSIS LEADING TO ORGANS DAMAGE

Researchers from the Duke-NUS Medical School (Duke-NUS) and National Heart Centre Singapore (NHCS) made a breakthrough discovery that a critical protein interleukin 11 (IL11) is responsible for fibrosis and organ damage.

Fibrosis is the formation of excessive connective tissue, causing scarring and failure of bodily organs and the skin. It is a very common cause of cardiovascular and renal diseases, where excessive connective tissue destroys the structure and function of the organ with scar tissue. When vital organs such as the heart or kidney are replaced with scar tissue, it will ultimately result in organ failure and subsequently death.

Currently, more than 225 million people worldwide suffer from heart and kidney failure, and there is no treatment to prevent fibrosis. Compared to other Asian regions, the USA and Europe, Singapore has a higher prevalence of coronary artery disease, hypertension, and diabetes – the three most common diseases that lead to heart failure. Kidney failure is also an epidemic in Singapore, with about one new dialysis patient every five hours.

This breakthrough discovery of inhibiting IL11 to prevent heart and kidney fibrosis meant that there is now a way to potentially transform the treatment of millions of people around the world through developing first-in-class therapies to block IL11.



The researchers Prof Stuart Cook (right), Tanoto Foundation Professor of Cardiovascular Medicine and Director of National Heart Research Institute of Singapore, and Asst Prof Sebastian Schäfer (left), both from NHCS and Duke-NUS' Programme in Cardiovascular and Metabolic Disorders.

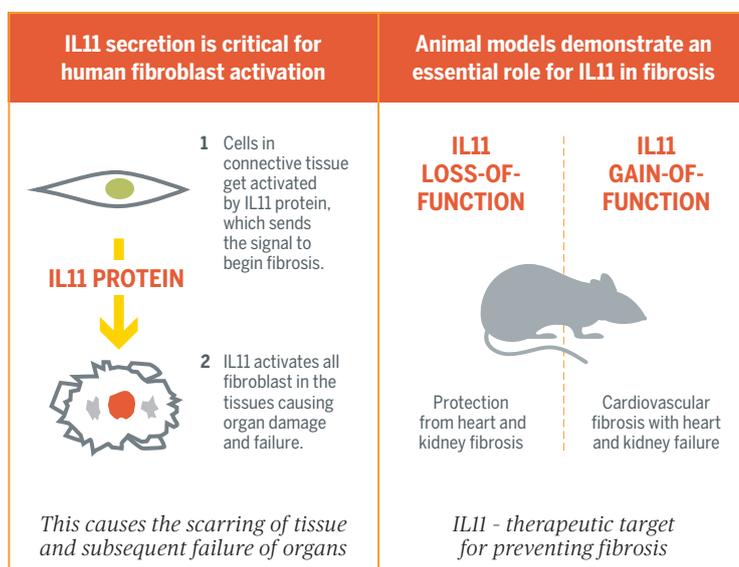
THE MISCONCEPTION OF CRITICAL PROTEINS

The research study, which began five years ago, was led by Prof Stuart Cook, Tanoto Foundation Professor of Cardiovascular Medicine and Director of National Heart Research Institute of Singapore, along with Asst Prof Sebastian Schäfer, both from NHCS and Duke-NUS' Programme in Cardiovascular and Metabolic Disorders. The findings overturned previous findings of IL11, which was thought to be harmless and dormant in fibrosis. Scientists had already known that a protein known as transforming growth factor beta 1 (TGFB1) was a major cause of fibrosis and scarring of body organs. However, when treatments to remove or reverse the TGFB1 protein are halted, patients suffered adverse side effects such as cancers or chest infections. These severe side effects are caused by the roles of TGFB1 in many processes unrelated to fibrosis.

During the study, Prof Cook and his team researched on more than 80 donated heart tissue samples from patients who underwent open-heart surgery at NHCS, as well as conducted trials on mice to demonstrate the role of IL11 in fibrotic disease. It is the first time such a large human cohort has been studied in this field. The results yielded the discovery that IL11 is required for the TGFB1 effect in fibrosis and the team was surprised that the importance of IL11 has been overlooked and misunderstood for so long.

“ Basically, IL11 is a “switch” that makes the TGFB1 protein fibrotic. If we “turn off” the IL11 fibrotic factor, TGFB1 doesn't work anymore and hence, there lies the hope to prevent fibrosis,” said Prof Cook.

Since identifying IL11 as a new drug target, Prof Cook and his team have been working towards developing a therapeutic antibody to deactivate the IL11 protein to prevent fibrosis.



DEVELOPING FIRST-IN-CLASS THERAPEUTICS TO TREAT FIBROTIC HUMAN DISEASES

With this breakthrough discovery, a new Singapore-funded biotechnology company called Enleofen Bio Pte Ltd has been set up. It holds the exclusive license to the research's intellectual property to develop first-in-class therapeutics for the treatment of fibrotic human diseases. Enleofen Bio aims to develop a potent new drug that inhibits IL11 by mid of 2019, said Prof Cook, with clinical trials starting by 2020.

Enleofen Bio was founded as a spin-out from NHCS, SingHealth and Duke-NUS with Series A funding. The initial discovery science and drug target validation was carried out at NHCS and Duke-NUS, funded by Prof Cook's funding from the National Medical Research Council, Goh Foundation and Tanoto Foundation.



CRITICAL PROTEINS

Interleukins are a group of proteins which handle communication between cells, and they regulate cell growth, differentiation and movement. They are particularly important in immune responses, inflammation and fibrosis.

Transforming growth factor beta 1 (TGFB1) is a kind of protein which plays an important role in growth and development, inflammation, repair and host immunity.

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NHCS CALL CENTRE

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Fax **(65) 6222 9258**
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Fax **(65) 6844 9030**
Email **nhcs@nhcs.com.sg**

NATIONAL HEART RESEARCH INSTITUTE SINGAPORE (NHRIS)

NHCS is involved in a wide range of cardiovascular research projects and clinical trials to improve diagnostic and therapeutic modalities for our patients. The NHRIS was established to bring cardiovascular research to new heights through NHCS' strategic collaboration with the Duke-NUS Cardiovascular and Metabolic Disorders Signature Research Programme. The NHRIS seeks to transform cardiovascular medicine via the power of basic and clinical research. This is in line with the NHCS' academic medicine journey, seeking to improve the lives and outcomes through enhanced patient care, education and research through its Cardiovascular Academic Clinical Programme.

OUR KEY RESEARCHERS – CORE & THEME RESEARCH

Prof Stuart Alexander Cook	<i>Genomics & Bioinformatics Scientific Lead Heart Functions & Genetics Theme Lead</i>
Prof Carolyn Lam	<i>HFpEF & Women's Health Theme Lead</i>
Prof Derek Hausenloy	<i>Heart Protection Theme Lead</i>
Assoc Prof Yeo Khung Keong	<i>Clinical Sciences & Statistics Scientific Lead</i>
Asst Prof Calvin Chin	<i>Imaging Scientific Lead</i>
Dr Wei Heming	<i>Experimental Electrophysiology Theme Lead</i>
Dr Ye Lei	<i>Disease Models Scientific Lead Endothelial Cell Biology Theme Lead</i>
Dr Zhong Liang	<i>Cardiovascular Bioengineering Theme Lead</i>
Dr Ang Hui Ying (Acting)	<i>Medical Technologies Theme Lead</i>
Mr Edmund Pua	<i>Biospecimen & DNA Scientific Lead</i>
Dr Gao Fei	<i>Principal Biostatistician</i>
Dr Katherine Teng	<i>Senior Research Fellow (HFpEF & Women's Health Theme)</i>
Ms Tay Wan Ting	<i>Biostatistician (HFpEF & Women's Health Theme)</i>

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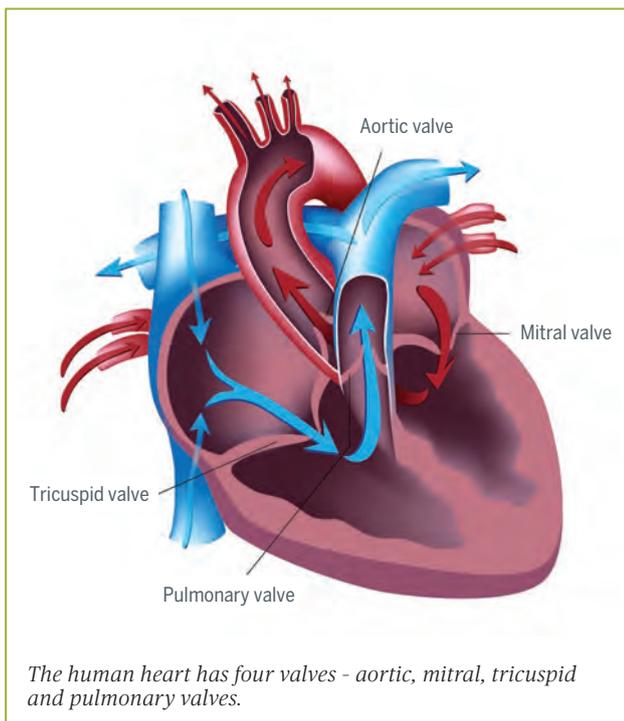
NEW PROCEDURE TREATS CONGENITAL HEART DEFECT WITHOUT OPEN-HEART SURGERY



National Heart Centre Singapore (NHCS) has introduced a minimally invasive procedure – Melody Transcatheter Pulmonary Valve (TPV) Implantation – and its first two patients have successfully undergone this therapy in last June.

Our heart has four valves, which are thin membranes or “flaps” that regulate blood flow in our body. As our heart muscle contracts and relaxes, our heart valves open and close to allow blood flow in and out of the heart chambers. Sometimes, problems with the heart valves may occur, either as a result of infections, degeneration, or congenital abnormality.

Tetralogy of Fallot, in particular, is a congenital heart defect and is one of the most common congenital heart diseases. Patients with this complex heart defect are born with four heart defects, one of which is that of the narrowing of the tract from the right ventricle to the main blood vessel to the lung. Currently, NHCS has more than 300 patients with the condition, and the number is expected to increase. These patients often have to undergo multiple open-heart surgeries throughout their lifetime.

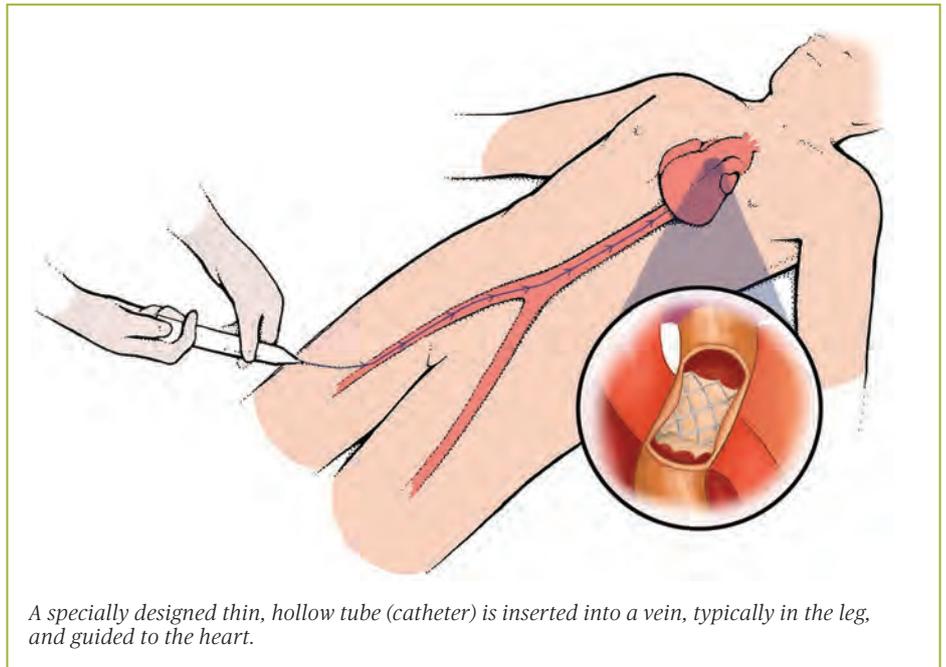


OUR FIRST PATIENT

27-year-old Alvin Poh is one such patient.

Born with this congenital heart defect, Alvin underwent his first open-heart surgery when he was merely two years old. Just when he was about to reach the age of 21, a routine heart check-up showed that his heart valve had started failing again and he was diagnosed to have severe pulmonary valve regurgitation. This meant that his heart valve was leaky and could not close properly. This led to a second open-heart surgery in 2013 to replace the pulmonary valve. With the newly replaced valve, Alvin had expected that he would not have to undergo another heart valve replacement surgery for another ten years. Unfortunately, in his final year of university in 2016, Alvin fell really sick. He was hit with a bout of recurring fevers and coughs, and had to be admitted into the hospital. It was then that doctors discovered that his condition was life-threatening and he had infective endocarditis, a type of valve infection, which destroyed most of his pulmonary valve which was replaced in the earlier open-heart surgery. Left with no choice, Alvin underwent his third open-heart surgery to replace the damaged valve. His ordeal was not over, as a review five months later showed high pressure readings from his replaced pulmonary valve on the echocardiogram. Alvin was diagnosed with pulmonary homograft stenosis, where his heart valve’s flaps had thickened and caused the opening of the valve to become narrow. Despite undergoing a heart catheterisation study and valvuloplasty (ballooning) to expand the constricted valve, Alvin’s condition did not improve. Although it is not uncommon for patients with similar heart condition as him to undergo multiple surgeries, Alvin was still hopeful that he did not need to undergo another surgery soon. Unfortunately, this was not so. Alvin was faced with the possibility of yet another open-heart surgery to replace his pulmonary valve.

Asst Prof Tan Ju Le, who is Director of the Adult Congenital Heart Disease Programme and Senior Consultant at the Department of Cardiology, NHCS, has been Alvin's attending doctor since his second surgery. She knew that every open-heart surgery brings increased risks and complications due to the internal scarring from previous surgeries. Asst Prof Tan was also concerned that Alvin already had three open-heart surgeries, and that he has barely recovered from his last operation, thus a fourth surgery would definitely pose a higher risk on top of his already tired mind, heart and body. It was then that Asst Prof Tan proposed a novel alternative treatment that was relatively new to the Singapore medical scene – the Melody TPV.



A specially designed thin, hollow tube (catheter) is inserted into a vein, typically in the leg, and guided to the heart.

MELODY TPV – THE MINIMALLY-INVASIVE PROCEDURE

The minimally-invasive Melody TPV procedure can replace leaky or narrowed pulmonary valves with a specially designed Melody valve attached to a thin, hollow tube (catheter) that is guided to the heart through the vein, without the need for an open-heart surgery. Once the Melody valve is in the right position, the balloon will be expanded to deliver the valve and blood flow is directed between the heart and the lungs. The Melody heart valve is made from a cow's neck vein that is attached to a wire frame.

Melody TPV is an alternative treatment option to treat a failing pulmonary surgical valve. Although it does not replace open-heart surgery, it has been proven to effectively delay the need for the next surgery. This therapy also reduces the long recovery period and pain that generally come with an open-heart surgery; it has been shown to improve symptoms as well. While the first Melody TPV procedure was done in Singapore only in 2016, it was first performed in London in 2000, and has now been implanted in more than 10,500 patients worldwide.

Alvin eventually decided to go for the new Melody TPV procedure in June last year and he was discharged soon after, just after five days. He has been recovering well since and was relieved that he could avoid another open-heart surgery.

“The new therapy can make a huge impact on patients’ lives, as is the case with Alvin where we can definitely see an improved quality of life since open-heart surgery brings about significant risks, pain, stress and discomfort. Over time, we hope to educate more patients on effective and better treatment options such as the Melody TPV therapy,” said Asst Prof Tan.



Asst Prof Tan Ju Le, NHCS, with her patient Mr Alvin Poh, at a recent Adult Congenital Heart Disease support group session.

“‘Hope’ is what I felt – being able to see that there is light in all of the darkness. The Melody TPV procedure allowed me to carry on living life to the fullest and spending time with my loved ones, and I’m eternally grateful for that!”

**Mr Alvin Poh
Patient of NHCS**

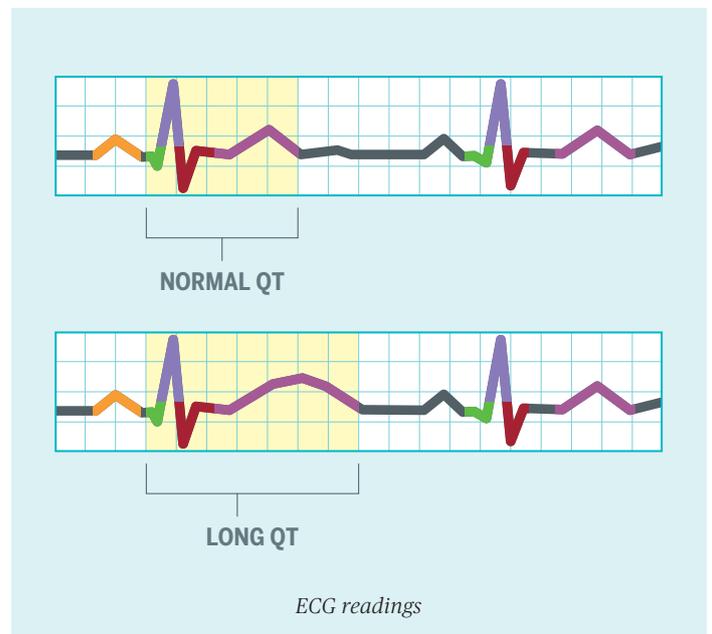


ERRATIC HEARTBEATS NO MORE

Researchers found a drug that can reverse the effects of Long QT Syndrome (LQTS) type 2, providing patients a possible alternative treatment other than having an implantable cardioverter defibrillator (ICD).

A complex electrical system exists in the heart, triggering each cell in the heart's muscle to contract at regular intervals, pumping blood in and out of the heart to the lungs and the rest of the body.

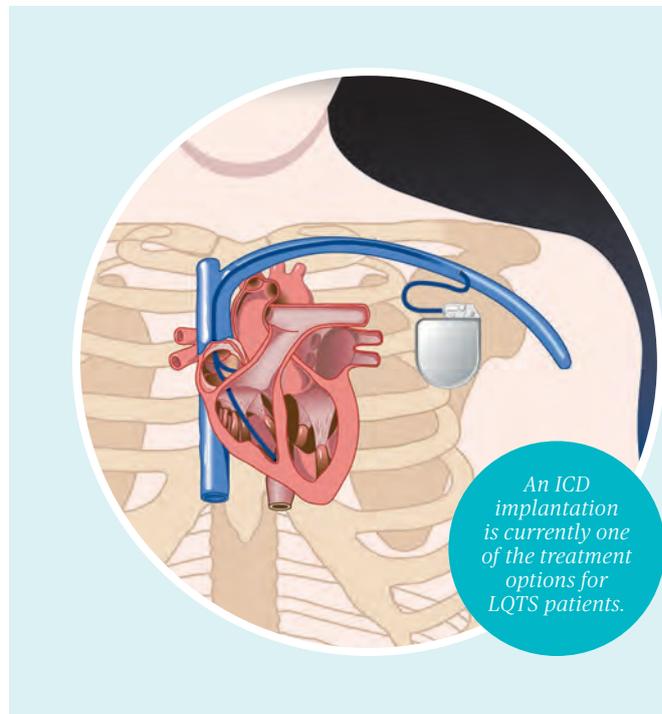
These electrical signals travel from one cell to another in the heart via signalling pathways in a precise and co-ordinated manner, led by a master electrical group of cells called the pacemaker. Should another aberrant group of cells take over this function and trigger a beat away from the pacemaker group of cells, this can potentially initiate Ventricular Tachycardia (VT) or Ventricular Fibrillation (VF). Serious abnormal heart rhythms like VT or VF are life-threatening and can cause sudden cardiac death.



LQTS is an inherited condition characterised by a prolonged QT interval that is measured via an electrocardiogram (ECG). A lengthened QT interval is a known marker for potential arrhythmia (erratic and fast heartbeat) and therefore also a risk factor for sudden cardiac death, especially among the young, which this condition affects. Moreover, patients sometimes do not display any symptoms prior to the first arrhythmic attack, which sometimes can be proven fatal.

LQTS affects approximately one in every 5,000 individuals worldwide and there are 13 types of LQTS, with types 1, 2 and 3 being the most common. LQTS type 2 is caused by mutation in the hERG (human ether-a-go-go related gene), and those with a family history of LQTS are at higher risk of inheriting the condition. A disorder of the hERG ion transportation mechanism causes the heart cells to be electrically unstable, making the heart prone to VT or VF. If left untreated, the consequence can be severe and even fatal.

Patients with LQTS are usually advised to avoid strenuous activities, and treatment options for LQTS include medications such as beta-blockers which can slow down the heart rate, and ICD implantation which can detect cardiac arrhythmia and deliver electrical shocks to restore a normal heart rhythm when necessary. Whilst the beta-blockers and ICD implantation help patients with LQTS reduce the risk of serious arrhythmias and prevent sudden cardiac death, both treatment options merely reduce the risk of VT or VF but they do not treat the underlying condition.



THE DRUG THAT REVERSES THE EFFECTS OF LQTS

Researchers from National Heart Research Institution Singapore (NHRIS) have discovered a drug that can reverse the effects of LQTS type 2, which can potentially remove the risk of arrhythmia in affected LQTS patients. The team used a novel platform for drug discovery and validation by utilising re-programmed stem-cells-derived beating heart cells obtained from the skin of five LQTS type 2 patients as well as two healthy individuals serving as “controlled” patients for benchmarking purpose. This platform allowed the researchers to test drugs directly on beating and functioning cardiac cells with the same genomic background of the actual patients. Tests involving a variety of drugs were conducted on these heart cells for the drug efficacies in controlling arrhythmias.

During the tests, the cells derived from LQTS patients were shown to easily develop VT and VF when stressed. However, a drug known as Lumacaftor was found to stabilise the cells by reversing the hERG transportation disorder found in these cells, which in turn reversed the prolonged QT measured in these cells, effectively reducing the risk of abnormal arrhythmias.



(From left to right) Dr Winston Shim, Senior Research Fellow, Assoc Prof Philip Wong, Deputy Director and Dr Krishan Ramachandra, Research Fellow, from NHRIS who made the drug discovery using the novel platform.

Lumacaftor is currently available commercially to treat cystic fibrosis, an inherited condition characterised by the accumulation of mucous and fluids in the lungs at birth. Interestingly, cystic fibrosis is caused by the same derangement of the hERG transportation of ions that occurs in the heart cells of LQTS type 2 patients.

“We are seeking potential collaborations with industry partners to conduct clinical trials to test if the drug can lower the risk of arrhythmias in the hope of developing a potential new treatment for LQTS patients,” said Assoc Prof Philip Wong, Deputy Director of the NHRIS and also a member of the research team.

This research work was published in the European Heart Journal with an accompanying editorial on the use of the novel platform, a form of precision medicine, for drug discovery.

THE RAREST GIFT – A NEW HEART

The number of heart donors in Singapore had steadily increased over the years, since the last Human Organ Transplant Act (HOTA) amendment in 2009. Yet, out of the total donated hearts received, only 20% to 30% of them are suitable for heart transplant.



Organ donation after brain death is on a voluntary basis in most other countries such as Australia, Europe or the United States of America. However, such voluntary donation remains uncommon in Singapore until a major amendment of the HOTA in 2004 mandating the compulsory donation of the heart, liver, kidneys and cornea in patients who have been certified to be brain dead, unless they have opted out of it prior to their demise. In spite of this, suitable donor hearts for transplantation have been few and far between.

**On average, only
TWO TO FOUR
HEART TRANSPLANTS
are performed each year in Singapore at the
National Heart Centre Singapore (NHCS).**

There are several obstacles to increasing the number of heart transplants performed in Singapore. Asst Prof Lim Choon Pin, Consultant at the Department of Cardiology, NHCS, explained that not only has the execution of the HOTA been challenging due to resistance to the retrieval of the organs by grieving and distraught relatives, the majority of potential donor hearts have been rendered unsuitable due to the presence of coronary artery disease in these potential donors as we see increased incidence of cardiovascular risk factors such as diabetes, hypertension or high cholesterol which lead to a decline in the quality of the hearts. Hence, the number of patients with end-stage heart failure on the heart transplant waiting list grows year on year.

To combat the lack of donor hearts, NHCS has implanted 90 artificial heart pumps, known as Ventricular Assist Devices (VADs), to keep patients alive while awaiting heart transplant since 2009. Patients undergo a major high-risk open-heart surgery to have this pump implanted within their chest and connected to their heart. The outcome is a wire that sticks out of their upper abdomen and is connected to a controller linking them to external electrical power supply in the form of batteries. While this pump has the ability to give them an improved effort tolerance and the energy to perform daily tasks and even exercise, there are significant lifestyle adaptations that need to be made to live with this pump. In Singapore, the survival rate of patients on VAD support is 87% at five years. Ultimately, the pump still has some significant disadvantages and risks of complication; thus, a heart transplantation is still the preferred long-term solution.



The Ventricular Assist Device is implanted into a patient's chest and connected to an external controller and batteries to help the heart pump blood around the body.

Image courtesy of HeartWare, Inc.



Serene Lee (extreme right), NHCS heart transplant patient, along with her heart donor's parents, Mr and Mrs Mark, who were visiting NHCS for the first time.

A NEW LEASE OF LIFE

Ms Serene Lee, 37, is a part-time clinic assistant who has been volunteering at NHCS and overseeing the heart failure patient support group for many years. She had dilated cardiomyopathy, a disease of the heart muscle which causes weakening of the heart and inability to pump blood efficiently. She was one of many patients on the waiting list for heart transplant and for years, she had to depend on VAD support until a suitable heart came along. When she finally underwent a heart transplant in 2015, she could not believe that she had been given a second chance at life. Her heart donor, a nursing student from Malaysia by the name of Ms Carmen Mark, had died after suffering an arterial rupture in her brain at the age of 18 and her parents had given their consent for Carmen's organs to be donated.

Somehow, as fate would have it, Serene did some sleuthing and managed to find out who her donor was. She finally plucked the courage to contact Carmen's parents, Mr and Mrs Mark, late last year. Since the bittersweet reunion, they had been coming forward to actively share their stories and raise awareness about organ donation.

Just last November, Serene brought Carmen's parents to NHCS to visit for the first time. Carmen was a recipient of the NHCS nursing scholarship and would have begun her nursing profession at NHCS upon graduation, had she not met with her unfortunate fate. Mr and Mrs Mark knew that they had to visit NHCS, just to see how the place is like, a place where both Carmen and Serene shared a close affinity to.

Mr Mark shared that it had not been an easy decision to donate Carmen's organs. He had initially gone through some internal struggle himself and admitted to facing some resistance from his own family before finally consenting to donate Carmen's organs. Deep down, Mr Mark knew that this was what Carmen had wanted as she had always wanted to help others, even after her death by donating her organs. He has plans to set up a foundation under her daughter's name to let her legacy live on. He believes in spreading love and kindness and these are values he had imparted to his daughter since she was a child.

There are currently more than 20 patients on the heart transplant waiting list and the average waiting time is typically three to four years, with some patients even waiting for as long as eight years. Asst Prof Lim revealed that the majority of heart failure patients who are on the list usually would not survive the wait, if not for the VAD. A successful heart transplant surgery will give the patient a good chance of leading a relatively normal life for at least the next 10 years. The average survival of heart transplant recipients in Singapore is 57.4% at 10 years, as opposed to chances of survival of less than 50% at one year for a patient with end-stage heart failure. Majority of the heart transplant recipients in Singapore have returned to a good quality of life, spending invaluable time with family and friends, and able to carry out daily activities without impairment. The longest living heart transplant recipient in Singapore has had over 30 years of life extended.

A good heart is not easy to come by, but what can help the lack of donors' heart situation is by encouraging people to adopt a more receptive mindset towards organs donation.



Team Harmony having a go at the soccer table, showing off some great teamwork.



Team Resilience having some fun, posing during a team cheer practice session.



Team Teamwork doing a jump shot, believing they will ace with 'flying colours'.



A gathering of some of the H.E.A.R.T runners who have completed the Ekiden race early.



Prof Aaron Wong of Team Empowerment having some selfie fun during the race.

RUNNING FOR A GOOD CAUSE – NHCS HEART TO HEART RUN

Five spirited and dedicated teams from National Heart Centre Singapore (NHCS) and Changi General Hospital (CGH) banded together and ran for a good cause at the Standard Chartered Singapore Marathon (SCSM) on 3 December 2017 to raise funds for patient care, research and education. #NHCSH2HRUN

Five teams, each led by a senior management, comprising 30 runners from NHCS and CGH recently participated in the 42.195 km Ekiden relay race of the marathon to raise funds for the NHCS Heart To Heart Fund to help improve the care for NHCS heart patients, and further cardiovascular research and education. Inspired to run for a worthy cause, it's not all just hard work and no play for our runners. Amidst the training at the gym and going for runs, our runners took time to bond with one another, building up the camaraderie and even came up with their own team cheers!

Even their team names reflected the values of **H**armony, **E**mpowerment, **A**chievement, **R**esilience and **T**eamwork (H.E.A.R.T) to bring hope to heart patients through the runners' spirit of positivity and determination to raise funds for the NHCS Heart To Heart Fund.

During the wee hours of the morning of 3 December – the race day itself – our five runners of the first leg of the Ekiden relay joined the first runners of 383 other Ekiden teams at Orchard Road, the starting point of the race. The Ekiden race route consisted of five other points at Hong Lim Park, Marina Barrage, East Coast Park, Marina East Drive and Gardens by the Bay, before finishing off at the Padang. All five H.E.A.R.T teams completed the Ekiden race well before noon, with Team Achievement scoring the best record, coming in at the 29th position of 388.

All in all, the five teams have raised a total of S\$32,450 for NHCS Heart To Heart Fund. Kudos to the runners and a big 'thank you' to all who had supported them!



Congratulations to Team Achievement, led by Prof Stuart Cook (right), who managed to finish at the 29th position in the Ekiden race.



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NHCS PUBLIC FORUM – HEART ATTACK

Heart disease is one of the leading causes of death in Singapore but many of us still do not know much about heart attacks or the symptoms. Our cardiologists will share on how to recognise, prevent, diagnose and treat a heart attack, as well as therapies if you had unfortunately suffered from one. Come and join us!

Date: 14 April 2018, Saturday
Time: 1.30pm – 5.00pm
Venue: Lecture Theatre, Level 7, National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609
Fee: S\$6.00

Limited seating, pre-registration required.
Registration closing date: 2 April 2018.

NHCS HEART CARE SYMPOSIUM – ATRIAL FIBRILLATION

This symposium is targeted mainly at General Practitioners and doctors who are interested to learn more about atrial fibrillation, abnormal heart rhythm characterised by rapid and irregular beating.

Date: 26 May 2018, Saturday
Time: 12pm – 4pm
Venue: TBA (Kindly check out our website link above for the latest updates.)

Free admission. Limited seating, pre-registration required.

APPOINTMENTS



**ASSOC PROF
DING ZEE PIN**
Advisor, Echocardiography



**ASSOC PROF
EWE SEE HOOI**
Director, Echocardiography



**ASST PROF
LIM SEE LIM**
Director, Operating Theatre



**DR CHAKARAMAKKIL
MATHEW JOSE**
Acting Director, Cardiothoracic Intensive Care Unit



DR ONG BOON HEAN
Acting Director, Lung Transplant Programme



**DR LOH WEI-TSEN
KENNY**
Head and Consultant, Department of Cardiothoracic Anaesthesia
Subspecialty interest: Cardiothoracic Anaesthesia

PROMOTIONS



**ASST PROF CHONG
THUAN TEE DANIEL**
Senior Consultant, Department of Cardiology
Subspecialty interest: Electrophysiology and Pacing



**DR CHAN LIHUA
LAURA**
Consultant, Department of Cardiology
Subspecialty interest: Heart Failure



**DR CHUA CHI MING
KELVIN**
Consultant, Department of Cardiology
Subspecialty interest: Electrophysiology and Pacing



DR GO YUN YUN
Consultant, Department of Cardiology
Subspecialty interest: Echocardiography and Cardiac Magnetic Resonance Imaging

ADVISORS

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Prof Koh Tian Hai

MEDICAL EDITOR

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